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A COMMENTARY ON CURRENT LITERATURE

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IN a recent very interesting paper, Warthin¹ discusses the different manifestations of syphilis as seen in the two sexes. In women, primary lesions are comparatively rarely observed by the physician or suspected by the patient. The anatomical arrangements make the female genitals less frequently and less easily inspected by the patient herself than is the case in the male sex. A lesion, therefore, which might attract the attention—if not the suspicion—of a man, is most likely to remain unnoticed by a woman.

In Fournier's experience the sites of female genital chancres were, in order of frequency: labia majora, labia minora, fourchette, urinary meatus, cervix, introitus vaginæ, clitoris, and vagina. There is a general tendency among syphilologists to suspect that chancres of the cervix are much more common than the text-books indicate. More such lesions would undoubtedly be recognised, especially in Venereal Diseases Clinic work, if all cervical erosions seen on speculum examination were investigated by the dark-ground method for the presence of the *Treponema pallidum*. A solitary cervical erosion, the margins of which do not encroach upon the lips of the external os, must always be regarded with grave suspicion. That suspicion should invariably be either allayed or confirmed by a microscopic examination. It is an excellent rule when making the speculum examination of a woman suffering from vaginal discharge to investigate by the dark-ground, material from any cervical erosion which may be present.

The genital primary lesion in women is usually smaller, less indurated, and more ephemeral than in men. Only comparatively seldom does it exhibit the classical Hunterian characteristics. As Warthin points out, there is frequently observed upon the cervix, clitoris, or

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urinary meatus, vegetative lesions strongly suggestive of carcinoma. These are simply large hypertrophic chancres—cauliflower-like in appearance—and showing on examination numerous treponemata. A higher degree of suspicion—especially among gynæcologists—and a more frequent use of the vaginal speculum and the microscope would lead to a larger proportion of early infections in women being recognised.

The general secondary cutaneous manifestations are as a rule much milder in women ; and frequently these are almost exclusively confined to the genital and anal regions. For this reason it is at times a matter of some difficulty to decide whether a genital papular lesion is really a primary chancre or a secondary manifestation. Warthin emphasises the fact that constitutional symptoms—fever, headache, anæmia—are more common and more severe among women. According to his findings there also appears to be a greater involvement of the viscera among females than among males as demonstrated by pathological examination. Marked clinical signs of such involvement, however, especially in respect of the cardio-vascular and central nervous system, are much more common among men.

I imagine that most clinicians will agree that when dealing with husband and wife, where the same strain of organism is involved and the same time-factor exists, the man appears to be more susceptible to central nervous system syphilis, and the woman to visceral and cardio-vascular. Moreover, the wife seems to respond to treatment better and more quickly than the husband both clinically and serologically. There would appear to be no room for doubt but that “femininity” or “female-ness,” and especially if it is associated with pregnancy, exerts a distinctly inhibitory effect upon syphilis. Pregnancy may cause not only a clinical, but even a serological, screening of the disease. It is important to realise that in such cases the action of the play is still going on unseen ; and that if observation be maintained, the curtain will rise again upon another act of the tragedy.

There would appear to be something in the female “make-up” which is capable of taking the edge off the virulence of syphilis—of causing a condition of *endosyphilis* where clinical signs are absent and where even the unprovoked serological test may give a negative

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result. Some years ago Montgomery² suggested as an explanation that this element of female protection is due to the secretion of iodothyron by the thyroid gland which is, as a rule, more active in women than in men. The effect of iodothyron, though small, is also prolonged, and is exerted continuously ; and it is certainly possible that that secretion may have some influence in inhibiting the activities of the *Treponema pallidum*.

Brown and Pearce³ showed that rabbit syphilis supervening upon a genital inoculation practically coinciding with conception differs very materially from the infection induced in a normal animal. The pregnant animal appeared to have a defensive mechanism developed on account of that condition, and in such an animal little or no clinical signs of the disease become manifest. It would seem probable that the chief factors in producing this resistance to syphilis are changes occurring in the syncytial and placental tissues. My view is that the increase of immunity is due rather to an increase of antibodies in the new tissues of pregnancy rather than that pregnancy stimulates the general antibody-producing tissues.

Chopra, Gupta, and Mullick⁴ report that they have been using a new aromatic bismuth preparation and have given it intravenously in the treatment of framboesia, syphilis, and filariasis. They report four cases of framboesia so treated with striking results, the lesions disappearing after four injections at weekly intervals in doses of 0.05 ; 0.1 ; 0.15 ; and 0.175 gramme.

The preparation is stated to be a sodium salt of papamino-phenyl-bismic acid in combination with urea, and to contain 51.1 per cent. of bismuth. It has been already pointed out in these Reviews and elsewhere that the intravenous administration of bismuth or any of its salts in the treatment of syphilis is not only wrong in principle, but is dangerous in practice. In the recent Cameron Prize Lecture at the University of Edinburgh this summer, by Levaditi on "Recent Advances in the Chemotherapy of Syphilis," this was emphasised. Levaditi stressed the point that bismuth salts show a relatively high toxic action when given intravenously. Furthermore, the mode by which bismuth acts upon the *Treponema pallidum* is that it is activated by the body tissues into a bismo-protein called *bismoxyl*. The power of tissues to transform bismuth into bismoxyl depends upon their content

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of glutathione—*bismogene*. It has been shown in the experimental syphilis of rabbits that bismoxyl cures syphilis not merely by stimulating tissue and general immunity reactions, but by an actual destruction of treponemata. Levaditi states that the therapeutic action of bismuth varies directly with the quantity of bismoxyl circulating in the body. This is termed the *tissue metallic potential*. It would appear that this potential is higher when insoluble salts are used rather than the metallic bismuth. The intravenous injection of bismoxyl itself would be a sound procedure ; but the intravenous injection of any bismuth compound or salt appears to be essentially wrong. The only reason why salvarsan or its substitutes is given intravenously is on account of the pain usually caused by intramuscular injection. There is no doubt but that when they are given intramuscularly the therapeutic effect is much greater. The pain and discomfort from the intramuscular administration of bismuth is trivial and often non-existent, and there seems no adequate reason, therapeutic or otherwise, why it should be given by the dangerous and toxic intravenous route.

McDonagh⁵ has for quite a long time insisted that the *Treponema pallidum* is only one stage in the life-cycle of the organism to which he has given the name *Leucocytozoön syphilidis*. He is of the opinion that the treponema is the male gamete of a sporozoan parasite, and that the other stages of the organism can be shown by different staining methods. McDonagh's work has not been generally accepted, chiefly because the *Treponema pallidum* can be cultured for many generations and only the spiral form found. Of course it is possible that culture *in vitro* retains the organism in the form of the treponema only, and that quite a different state of affairs may occur *in vivo*. The acceptance of McDonagh's views would certainly in many ways explain several puzzling problems in connection with syphilis and its transmission.

With reference to this question, Wile⁶ in a paper on the spirochætal content of the spinal fluid in tabes, general paresis, and cerebrospinal syphilis, points out that the organisms have been successfully demonstrated in the spinal fluid in isolated instances only. Wile did a series of experiments consisting of injecting the spinal fluid from cases of cerebrospinal syphilis, tabes, and G.P.I. into the rabbit's testes. In every case a very thorough

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examination of the fluid failed to reveal treponemata. Syphilis occurred in the experimental rabbits in over 60 per cent. of experiments. The failure to find treponemata in the cerebrospinal fluid suggested to him the possibility of the organism existing therein under some other form, and only reassuming the aspect of a treponema when transferred to the tissues of the rabbit.

Levaditi, Scoehm, and Sanchis-Bayarri⁷ now believe, as the result of recent investigations, that the *Treponema pallidum* is only one of the stages in the developmental cycle of the syphilitic virus. They find that the lymph glands of animals inoculated with syphilis may show no treponemata ; but that such lymph glands prove virulent when inoculated into a fresh animal. They think that the organism exists in these glands in some form other than that of the treponema. They suggest that this phase of the virus is more resistant to treatment than the treponemal form, and that this is the culprit in endosyphilis and in those forms of the disease as it affects the central nervous system in which no organism can be found.

If the existence of a developmental cycle for the virus of syphilis is established, the priority for the suggestion or the discovery most certainly belongs to Maclellan,⁸ as was pointed out in this JOURNAL, Vol. I., p. 121, 1925.

In a report of fifty-two cases of subacute endocarditis, Sumbal⁹ found that the Wassermann test gave a positive result in eighteen instances. He believes that a syphilitic infection reduces the defensive power of the reticulo-endothelial apparatus, and so paves the way for a subacute endocarditis. These cases are characterised by a hæmorrhagic diathesis, a prolonged course with a low temperature curve, and by a good response to anti-syphilitic treatment. He recommends a routine Wassermann test in all cases of cardiac disease, since syphilis has a detrimental effect upon the course of any cardiac condition owing to the possibility that a subacute endocarditis is liable to occur.

In discussing the specific treatment of syphilitic aortitis, Doumer¹⁰ draws attention to the fact that bad effects occasionally follow the administration of arsenobenzol. Where the signs of cardiac failure are slight, arsenobenzol may increase them, and anginal attacks may be precipitated. His explanation is that these occurrences are due to irritation supervening upon the

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vascular congestion caused by the resolution of gummatous material and the consequent absorption of necrotic products. He points out that in such cases it may be necessary to discontinue arsenobenzol and carry on with bismuth. The writer's own view is that cardiovascular syphilis should be treated with bismuth alone in the beginning, reserving the arsenobenzols till later when the virulence of the infection has been somewhat blunted. Experience would seem to show that the effect of arsenobenzol in acute cases, and especially in those involving the circulatory system, is very frequently to aggravate the condition and to precipitate a late Herxheimer-like reaction. The true Herxheimer reaction is, with very little doubt, a reactivation of the disease ; and it occurs, as a rule, after the earlier injections. In this respect it differs from the condition described by Doumer, that generally taking place after the fourth or fifth injection. In the true Herxheimer, if treatment is continued, the phenomenon disappears. In the other delayed condition further treatment only makes things worse, and the general state of the patient gradually deteriorates. In cardiovascular syphilis, when arsenobenzol is administered at the beginning of treatment it assaults the syphilitic infection after the fashion of dynamite, scattering the *débris* far and wide throughout the interior economy of the patient and to his general disadvantage. Bismuth, on the other hand, may be compared to spade-work—more laborious, no doubt, but eminently safer and throwing much less strain upon the human mechanism. There is sometimes a tendency to forget when delivering the attack upon syphilis, that the enemy can be defeated without at the same time laying waste the country he has invaded. He can be turned out without setting fire to Moscow.

Harris ¹¹ points out that cardiac syphilis is a very common infection, but frequently goes unrecognised. There is no single sign or method of diagnosis by which cardiac syphilis can be distinguished. It is necessary to have recourse to every means available, physical signs, Wassermann test, electro-cardiographic examination, history, and symptoms.

In cardiac cases the disease is usually of some age, and for this reason the securing of a negative result to a blood Wassermann test does not rule out lues of the heart. Cardiac syphilis with a negative blood and a positive

cerebrospinal fluid is not uncommon. Harris maintains that it is possible in many instances to diagnose syphilis of the heart with much certainty from clinical evidence alone, and that in the majority of cases the evidence is such as to raise a strong suspicion. Two features are characteristic of cardiac syphilis: the involvement of the aorta and coronary arteries and also the myocardium. Harris contrasts this with the rheumatic valvular heart, in which but rarely is the muscle affected. Out of eighty-eight electro-cardiograms of cases of cardiac syphilis, only nine were normal; from the same number of rheumatic valvular heart cases, forty-two were normal. The important point is that where there is a valvular lesion with signs of myocardial involvement, the probability is that we are dealing with syphilis. The clinical picture in syphilitic valvular disease is always somewhat atypical of what would be found in a purely rheumatic case. It is not so clean-cut, and one finds such cases labelled "tired" or "irritable" heart. Harris very rightly emphasises the fact that an accentuation of the second aortic sound in the absence of high blood pressure, where there is a history of syphilis or a positive blood Wassermann test, is diagnostic of syphilitic aortitis and myocarditis. In the absence of any history of syphilis and in the presence of a negative blood test, it is highly suspicious; so much so that antisyphilitic treatment is indicated as a therapeutic test. There is no cardiac condition which may not be due to the *Treponema pallidum*. In Harris's experience the most characteristic symptom is cardiac pain. This was present in 70 per cent. of cases. It differs from the typical pain of angina in that it is not so intense, does not come on so suddenly, and as a rule differs in distribution. Pain referred to the gastric region is common, and may give rise to the suspicion of gastric ulcer.

The use of the electro-cardiograph is of great importance in the investigation of heart cases for syphilis. While the great majority of abnormalities recorded by the electro-cardiograph are not characteristic of syphilis, but merely indicate a damaged heart muscle, it is nevertheless an invaluable means of diagnosis, because frequently it is only by its means that we are able to discover that there is something wrong with the heart. In the experience of Harris, certain wavelets all over the electric line are not seen in any condition other than cardiac syphilis. He

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concludes a very interesting and instructive paper by recommending the Wassermann test as a routine procedure for all cases suffering from heart disease.

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